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Weak, physiologically patterned magnetic fields do not affect maze performance in normal rats, but disrupt seized rats normalized with ketamine: Possible support for a neuromatrix concept?

B.E. McKay [1], M.A. Persinger *

Behavioral Neuroscience Laboratory, Laurentian University, Sudbury, Ont., Canada P3E 2C6

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Abstract

The concept of a neuromatrix as a determinant of behavior proposes that complex neuroelectromagnetic patterns supported by specific spatial configurations of neurons underlie the generation of behaviors. When the pattern of neuronal connectivity is changed, as occurs during limbic epilepsy, neuroelectromagnetic patterns change in parallel to sustain behavioral output. Thus, a testable prediction of the neuromatrix concept is that the "normal" behaviors of animals with markedly reorganized neuroelectromagnetic patterns are vulnerable to specific stimuli that are ineffective when applied to a normal population. Because rats treated with ketamine after being induced to seize with pilocarpine exhibit behaviors indistinguishable from those of control populations despite marked changes in brain structure, they represent an ideal population in which to examine this hypothesis. Ketamine-treated pilocarpine-seized rats and normal rats were exposed continuously either to a complex sequence magnetic field or to control conditions during the acquisition of a radial arm maze task for 8 consecutive days. After 14 days of subsequent exposure to a frequency-modulated field (7–500 nT), during which time there was no training, the rats that had been induced to seize and had been exposed continuously to this magnetic configuration exhibited conspicuously slower response durations per arm than rats that had been induced to seize and exposed to control conditions or normal rats that had been exposed to either magnetic fields or control conditions. Thus, the behaviors of rats who have sustained multiple, discrete injuries throughout the brain may be seriously disrupted by the appropriate pattern of exogenous weak magnetic fields. Our results represent the first empirical support for the concept of the neuromatrix.
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1. Introduction

The concept of a neuromatrix that determines behavior involves three assumptions. First, all behaviors are generated by complex neuroelectromagnetic patterns supported by and compatible with microarrays or spatial configurations of neurons within brain space. Second, behaviors can be displayed only if the physical substrates of these complex spatial configurations exist within the brain. Third, different spatial configurations can support the same or similar neuroelectromagnetic patterns and hence generate the same behaviors. However, the behaviors generated by these different mosaics would be vulnerable to disruption by different stimuli because the intrinsic "natural frequencies" or resonances of the configurations would differ.

Temporal lobe epilepsy (TLE) in humans is associated with a marked reorganization of brain structure. The neuronal, electroencephalographic, and behavioral sequelae of TLE can all be reproduced in rodents with the pilocarpine epilepsy model [1–4]. Since the demonstration that the noncompetitive NMDA antagonist ketamine reduces mortality

* Corresponding author. Fax: +1 705 671 3844.
E-mail address: mpersinger@laurentian.ca (M.A. Persinger).
[1] Present address: Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada.

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in this model [5], ketamine has been shown to attenuate or abrogate many pilocarpine-induced sequelae. For instance, when administered following pilocarpine treatment, ketamine raises the threshold for afterdischarges, minimizes spike and wave discharges, reduces c-*fos* expression throughout the brain, and results in the expression of normal behaviors [6–15]. Ketamine has also been used successfully in the clinic to treat epilepsy [16].

We [17–19] have been investigating the behavioral effects of the multifocal loss of neurons that occurs within the rat brain following a single peripheral injection of lithium and pilocarpine [1] or a single larger dosage of pilocarpine [20]. We have found that rats that are injected with 100 mg/kg ketamine within 30 minutes after induction of seizures using lithium and pilocarpine display normal spatial learning and memory despite substantial multifocal brain damage. By comparison, rats that receive the neuroleptic acepromazine instead of ketamine display behaviors that were interpreted as severe impairments of learning and memory. Importantly, the quantitative values of the proportions of neuronal loss in both populations of rats were almost identical; only the spatial patterns of neuronal loss differed. Thus, the multifocal pattern of the damage in the ketamine-treated seized rats allowed the emergence of other functional associations within brain space because different subpopulations of cells survived, enabling the continued generation of "normal" behaviors [8,10]. This might be compared with the principle that the larger the number of cells in a mathematical matrix, the larger the number of combinations of patterns of values that could result in the same diagonal solution. The pilocarpine model, by destroying some pathways, leaving others intact, and resulting in normal behavior in ketamine-treated seized animals, provides an excellent test for the neuromatrix hypothesis [13].

We have previously shown that exogenous applications of magnetic fields were most effective when the waveforms of the magnetic fields were "complex" and "physiologically relevant" [21,22]. For instance, following training sessions in a conditioned fear paradigm, application of a theta-burst complex magnetic field, the structure of which was modeled after the theta-burst stimulation protocols known to be maximally effective in modulating hippocampal long-term potentiation (LTP) when administered via direct electrical stimulation, markedly reduced the magnitude of learning. In contrast, application of a conventional sinusoidal (noncomplex) magnetic field of the same intensity and same power-frequency spectrum had no effect. Thus, the complexity of the magnetic field, and the relevance of its structure to ongoing physiological processes, is paramount to the efficacy of the magnetic field in modulating behavior. As the neuromatrix is the superimposition of neuroelectromagnetic patterns on permissive configurations of neuronal patterns, novel organization of brain following seizures [23] should support novel neuroelectromagnetic patterns.

If the concept of the neuromatrix was valid, we predicted that exposure of rats that had received ketamine (following the induction of seizures) to complex magnetic fields should create a "virtual" neuroelectromagnetic matrix within the space occupied by the brain. When magnetic fields are applied following a period of synaptic reorganization, such as occurs with the learning of a radial maze task, this exogenous pattern, like a *zeitgeber*, would serve as a "structure maker" or organizer of the myriad of stimulus inputs that pass through the seizure-induced, modified synapses [23] containing the representation of the maze. However, once these patterns have been established, subsequent exposure to another complex magnetic field should erode this representation such that the distinction between previous spatial patterns (memories) and new spatial patterns would be less. As a result these seized rats would display poorer performance in learning a different pattern within the maze. Rats with a similar seizure history but not exposed to the other magnetic pattern should display behaviors comparable to those of controls.

The controls, because their brains are organized differently ("normally"), should not be vulnerable to the effects of the fields that specifically affected the seized rats that had been treated with ketamine. The brains of control rats would be dominated by such excessive redundancy from the endogenous neuroelectromagnetic patterns from larger aggregates of neurons that organization from exogenous fields would be masked. If these predictions were supported, then there would be additional evidence for the existence of the neuromatrix and, possibly, support for the validity of the contentions of about 15 to 20% of patients (n of about 1000) we have assessed over the years who have reported "enhanced sensitivity" to various forms of environmental magnetic fields (from 60-Hz appliances and particularly computers and computer screens) following mild brain injuries, even without loss of consciousness. These "subclinical" traumas, which in rats produce histologically verifiable alterations in the soma of about 20 to 50% of neurons within the penumbra of the force vector [24], may be more likely to promote minute or partial loss of neuronal populations within multiple, very small volumes throughout the brain such that the neuromatrix could undergo a functional reorganization.

2. Method

2.1. Subjects

Thirty-two male Wistar (Charles River, Quebec) rats, approximately 90–100 days of age, were employed as subjects. Before the study began they had been housed in groups of three (since approximately 60 days of age) in standard wire cages within rooms in which the temperature was controlled within 1° of 20 °C while relative humidity was about 40%. The light cycle was 12:12 with lights on at 0730 local time. All procedures were completed in accordance with the guidelines established by the Canadian Council on Animal Care.

2.2. Procedure

In two separate blocks (replicates) of experiments separated by 4 months, 16 rats were injected at 90 to 100 days of age with 380 mg/kg (1 ml/kg, subcutaneously) pilocarpine. The other 16 rats received isotonic saline. Immediately after the display of Racine stage V convulsions [25], defined as rearing, rapid forelimb clonus, and falling, the seized rats were injected subcutaneously with 100 mg/kg of the noncompetitive NMDA antagonist ketamine. Seizure onset time was within the normal range (for this age) between 25 and 35 minutes; there was no mortality. After this procedure, rats were returned to their home cages and given food mush and water for about 4 days or until they returned to consuming solid food [19].

There were eight seized and eight control rats in each of the two blocks of experiments. Ten days subsequent to injection with pilocarpine or saline, the rats were randomly assigned to one of two identical custom-constructed Plexiglas cages. Each cage measured $140 \times 33 \times 33$ cm and was divided into four equal cells. Two rats (one seized, one control) were placed into each cell. At the ends of the exposure cage were two identically balanced 39×39-cm coils, each consisting of 305 m of 30 AWG (Belden 9978) wire wrapped in a single layer 18 cm wide. The control cage was located in another room 10 m from the exposure condition during the first experiment, but was parallel to and 2.5 m away, within the same room as the experimental coil, in the second experiment.

Custom-constructed software operating on a Zenith XT computer was used to generate the complex magnetic fields. The software converted a waveform file (a series of 1000 to 10,000 lines) of digital values from 0 through 255 to analog equivalents of −5 V through +5 V, respectively. The voltage equivalent was propagated through one of the two coils (one activated coil, one inactivated coil) and emitted as a magnetic field. The software employed controlled the pixel duration of each point in the waveform (the length of time each line of the waveform file was propagated to the digital-to-analog converter), as well as the interval between successive applications of each waveform (magnetic stimulus). The mean intensities of the magnetic fields (multiple complex sequence field and frequency-modulated field) within the exposure cages were 510 nT (adjacent to activated coil), 93, 32, and 7 nT (adjacent to inactivated coil).

On the bases of our previous research and our assumptions of the mechanisms involved with the neuromatrix, we employed two complex waveforms in this study. Both had been designed for their physiological relevance and their similarity to what we assumed to be algorithms of essential neuronal activity. The first, a multiple complex sequence waveform [26], consisted of chains of discrete patterns, each of which has been shown to be bioeffective. The composite patterns, each presented for 200 ms in various combinations, are shown in Fig. 1. The horizontal axis refers to the successive increments of 1 ms that ultimately composed each pattern, whereas the vertical axis refers to the incremental values between −5 V and +5 V that reflect the equivalent numbers between 0 and 255 (128 = zero polarity) from the software from which the pattern was generated. The resultant pattern (see [21] for parameters) was composed of 10,000 points with the duration of each point set at 1 ms. The sequence, whose duration was 10 seconds, was presented every 1000 seconds (1 mHz) to simulate the general temporal patterns of calcium oscillations in cells [27] and the transition to infraslow potentials [28].

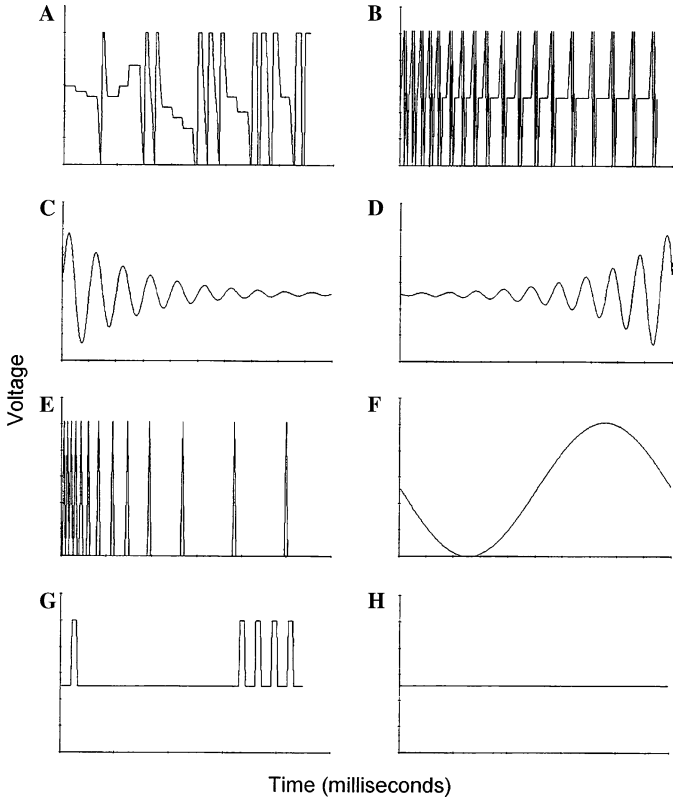

Fig. 1. The different patterns constituting the complex sequence magnetic field. Vertical axis refers to relative voltage (between −5 V and +5 V), and horizontal axis, to the successive 1-ms increments that ultimately composed the pattern. (A) burst-firing, (B) frequency-modulated or "Thomas pulse", (C) negative ringing, (D) positive ringing, (E) Fibonacci series, (F) slow wave, (G) long term potentiation (LTP) pulse, and (H) steady-state field. Note that the frequency-modulated (B) magnetic field was also a subcomponent of the complex sequence.

The second, a frequency-modulated waveform, consisted of blocks of spikes whose frequency within the waveform progressively decreased from about 16 to 10 to 7 to 5.6 Hz; every second spike within a block was presented at 56 Hz. The point duration of the numbers between 0 and 255 that generated the pattern was 3 ms; the interstimulus time between successive patterns was 3 ms. These parameters for this pattern have been shown to increase the probability of "spontaneous" overt limbic seizures in seized rats treated with acepromazine [29]. This redundant frequency-modulated pattern (Fig. 1B) was the same shape as that contained as a subcomponent of the multiple com-

plex sequence field, except the point durations were 3 ms instead of 1 ms.

The radial maze [30] consisted of a 60-cm-wide octagonal arena with 90×10-cm-wide arms radiating outward from each of the eight sides of the central arena. A 3-cm-diameter recessed food cup was present at the end of each arm. The maze was elevated 1 m above the floor. External cues, including shelving, tables, and posters on the wall, were provided to enable spatial navigation. The rats were tested by the procedure described by Vaillancourt and Persinger [10]. In brief, for any given block of an experiment, the same four arms contained a food reward and the other four did not.

The rat was given a total of 15 minutes to complete the task. The reinforcer was approximately 100 mg of crushed rat chow in the appropriate food cups at the ends of the arms. Number of entries into an arm that was never baited (reference memory), number of entries into the same arm during the same day (working memory), and total time to complete the task (retrieve food from each of the four baited arms) was recorded. The response interval was also calculated to accommodate subjects that did not complete the task each day. Response interval was calculated by dividing the total time required to complete the maze per session by the total numbers of arms entered per session.

The testing period, except for change of bedding every 3 or 4 days, was the only time the rats were removed from either the sham field or field conditions. Rats were tested in the maze only once per day after 23 hours of food deprivation. After 2 days of habituating to a schedule of 23 hours of food deprivation, rats in both blocks were subjected to the following procedures.

2.2.1. Acquisition phase during complex field exposures

During the first 8 days of training, half the seized rats and half the control rats were exposed continuously to multiple complex sequence magnetic fields, while the remaining rats were exposed to control conditions. Following each daily maze training period, rats were returned to their conditions within 1 minute of completing criterion, so that they were always within the field or control conditions during the critical consolidation periods. Our rationale was that the field would support the neuroelectromagnetic representation of the consolidation of the maze and be associated with it.

2.2.2. Different field, no training, food ad libitum

If our hypothesis about the neuromatrix was valid, then exposure to a different patterned field should interfere with long-term consolidation of the experiences that facilitated spatial localization of rewards within the maze. Consequently, after the acquisition phase, there was no maze training or testing for 14 days. For the first 10 days, one coil was activated, and during the last 4 days, the other coil was activated. However, during the entire period the rats were exposed to the frequency-modulated pattern, not the multiple complex sequence pattern. For 12 of the 14 days, food was available ad libitum. For the last 2 days, the rats were returned to the 23-hour food deprivation schedule.

2.2.3. Reversal training: no fields

Rats were trained for a reversal task during the second block of 10 days in the maze. For this period the four arms that had not contained food during the first (acquisition) block contained food, and those that had contained food did not. The rats were not exposed to any field conditions (all control conditions). We employed the reversal strategy rather than testing memory for the arms that had been always rewarded in the maze, to minimize the contributions of motor memory that occur over time when behaviors are overlearned. We hypothesized that the seized rats exposed to the frequency-modulated field should display a marked and conspicuous vulnerability. It would be manifested behaviorally as poorer or confused learning of a new spatial pattern in the maze.

2.2.4. Maze training and multiple complex sequence field: shift test

During the third block of 8 days in the maze, immediately following the previous reversal training, rats were exposed again to the multiple complex sequence field. It was activated immediately after the tenth session of the reversal training. We hypothesized that the seized rats exposed to the field should display shorter response durations (greater proficiency) because the original "exogenous matrix" had been reconstituted. The coil that had been activated last (with the frequency-modulated pulse) was activated for the first 4 days with the multiple complex sequence pulse, whereas during the last 4 days, the other coil was activated within the same magnetic pattern. If the original condition was required to increase proficiency for maze learning, then conspicuous improvement should occur suddenly after this implementation had occurred.

2.3. Statistics

Three way analyses of variance with one within-subject (repeated) measure (days) and two between-subject (control vs seized; field vs control) measures were completed for each block of trials that included: the 8 days of acquisition, the 10 days of reversal training, the first 4 days of the multiple complex sequence field, and the second 4 days (active coil reversed). Post hoc analysis involved paired *t*-tests and Tukey tests. All analyses were completed with SPSS software on a Vax 4000 computer.

3. Results

Although traditional reports of results from radial maze studies have emphasized the numbers of errors for reference memory and working memory and the total time required to complete criterion (consuming reward in the

four baited arms), these measures, although recorded, were not feasible to interpret in the present study. The rats that had been induced to seize, treated with ketamine, and then exposed to the complex magnetic field frequently did not complete the task during the allotted time of 15 minutes. Thus, by virtue of their inactivity, the ketamine-treated field-exposed rats made almost no working memory errors and, by failing to enter correct arms, reached the ceiling measure for reference memory errors. The rats that had been induced to seize, treated with ketamine, and then exposed to the control condition did not differ from normal rats. As in previous studies [8,10], the rats that had been induced to seize and treated with ketamine, but not exposed to a magnetic field, did not differ significantly from sham-exposed or magnetic field-exposed normal rats with respect to either number of reference errors, number of working errors, or time to reach criterion.

Consequently, to obtain data that could be analyzed systematically by the more informative parametric analysis, we employed the duration of responding. To satisfy the assumptions of homogeneity of variance, all daily (per arm) values for duration of responding were log (base 10) transformed prior to the analyses. Although the results did not differ appreciably from those obtained with raw scores, the values reported in this section involved the log base 10 transformations. However, for ease of interpretation, the reported means and SEM were always calculated from the untransformed data. They are illustrated in Fig. 2.

For block 1, the acquisition phase (Fig. 2A), there were no statistically significant differences between the rats that had been induced to seize and those that had not been induced or between the rats exposed to the field and those not exposed [both $F(1,28) < 3.24$, $P > 0.05$]. The change in duration of responding for the within-subject (days) factors was statistically significant [$F(7,196) = 7.71$, $P < 0.001$, $\eta = 0.22$], whereas all of the interactions between the between-subject effects and the repeated measure were not significant statistically [$F(7,196) < 1.36$].

For block 2, the reversal phase (Fig. 2C), there was a statistically significant interaction [$F(1,28) = 10.46$, $P < .01$, $\eta = 0.27$] between the induced and noninduced rats and between the field-exposed and non-field-exposed rats; the source of the interaction was the group induced to seize and then exposed to the field. Post hoc analysis indicated that the rats that had been induced to seize, treated with ketamine, and later exposed to the frequency-modulated field during the previous 10 days of no testing required significantly more time (about 5 to 10 times longer) per arm compared with the other three groups that did not differ significantly from each other.

The significant three-way interaction [$F(9,252) = 4.97$, $P < .001$, $\eta = 0.15$] between the two independent variables and the repeated measure was due primarily to the decreased response duration on the second day of reversal training for the induced/field-exposed group compared with most of the subsequent days. Additionally, the inter-

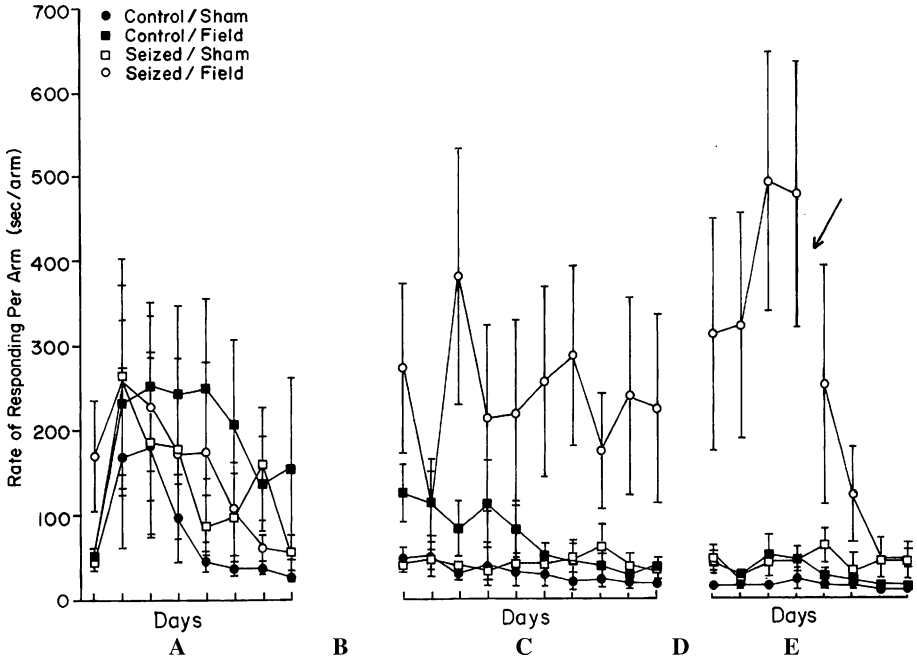

Fig. 2. Mean duration per arm for daily sessions in a radial maze task. Error bars indicate SEM. Rats were divided into one of four groups: normal rats that were not exposed to a complex magnetic field, normal rats that were exposed to a complex magnetic field, ketamine-treated seized rats that were not exposed to a complex magnetic field, and ketamine-treated seized rats that were exposed to a complex magnetic field. During the first 8-day block (A), rats were exposed to the complex sequence magnetic field or no field. After 14 days of exposure to the frequency-modulated field or no field (B), during which no maze training occurred, rats were trained for 10 days in a reversal task in the maze (C). Following a 1-day intermission (D), rats were again exposed to the original (multiple complex sequence) magnetic field but with different intensities (E). The arrow indicates the beginning of exposure to the initial intensities and direction of the multiple complex sequence.

action was rooted in the significant decrease in response duration for the control/field-exposed rats over the first 4 days of reversal training compared with the sham field groups (induced to seize or controls) that did not show these changes over time.

During the first 4 days of exposure to the complex sequence field (Fig. 2E), there was a statistically significant interaction between seizure history and exposure to the field [$F(1,28) = 15.99$, $P < 0.01$, $\eta = 0.36$] that was due to the longer response durations for the single group that had been induced to seize and exposed to the field, compared with the other three groups that did not differ significantly from each other. During the second 4 days (after the arrow in Fig. 2E), when the source of the complex sequence field was shifted to the opposite coil, a statistically significant [$F(1,28) = 5.51$, $P < 0.001$, $\eta = 0.35$] interaction between day, seizure history, and field condition was evident. This was due in large part to the improvement in response duration for the rats that had been induced to seize and exposed to the complex sequenced field compared with the improvements for rats subjected to any of the other three treatments.

4. Discussion

In previous studies we had shown that rats in which seizures had been induced with excessive cholinergic stimulation but treated with ketamine exhibited normal spatial memory and response durations despite extensive brain damage [8,10]. When compared with rats that had been treated following induction of these seizures by acepromazine, ketamine-treated rats displayed more damage within the amygdalohippocampal/anterior hippocampal transition area but significantly less damage within the central, lateral, and dorsal nuclear groups of the thalamus. The dozens of other structures, including cortical areas, did not display any significant differences in the proportions of damage between acepromazine- and ketamine-treated rats in which seizures had been induced.

In the present study rats that had been induced to seize and treated with ketamine shortly after induction displayed a marked sensitivity to the presence of specific complex magnetic fields during periods associated with long-term consolidation within brain space. During a reversal problem in the maze (Fig. 2C), these rats required about 6 to 10 times the amount of time to enter and exit each arm than did rats that had been induced to seize but had not been exposed to the fields. The latter rats did not differ from normal rats that had been exposed to either the field or control conditions.

The results are consistent with our model of a neuromatrix. Although the seized rats exposed to another complex field during the 14 days of no training after the acquisition phase had conspicuously slower response durations per arm than the other three groups, we cannot rule out the possibility of induced seizure activity. Rats that have been induced to seize and treated with ketamine have never been observed to seize overtly as do rats treated with acepromazine [17,18]. The latter rats display chronic and severe deficits for both maze acquisition and memory. We cannot exclude the possibility that the frequency-modulated fields may have increased electrical seizures [29] that simply were not overtly displayed (or observed) but were sufficient to affect maze behavior. If this occurred, then the more mundane "seizure-disruption" mechanism would supersede the concept of the neuromatrix as the most parsimonious explanation.

The seized rats that received the original intensity of the complex sequence field did not show immediate improvement following the reimplementation of this condition (after the arrow in Fig. 2E). If this exogenous organizer had been associated with the initial maze learning, then the rats should have improved immediately. Interestingly, when the coil that was initially activated was again the source of this field pattern, the rats quickly improved within 2 days to control levels, at which they had never been except during the acquisition phase. Obviously this may have reflected some delayed learning that would have occurred without the field. This effect was evident in both blocks of experiments.

Regardless of the potential mechanism, this study clearly demonstrated that the apparently "normal" maze behavior of rats that have been treated with ketamine after induction of seizures can be seriously disrupted by exposure to very weak complex magnetic fields. We have assumed that the enhanced response durations reflected deficits. We cannot exclude the possibility that other "qualitatively different" behaviors may have occurred that we did not measure or were not manifested because we did not employ the appropriate context. For example, we did not measure subtle indicators of vestibular-motor anomalies or control for the effects of the magnetic fields on motivational processes.

It may be noteworthy that our post hoc analysis of the behaviors as a function of the four ranges of intensities showed that the rats with the pronounced deficits had been the closest to the activated coils. These intensities (1–5 mG or 0.1–0.5 μT) are within the range encountered near computer terminals and other modern electronic equipment. Many of our patients, referred for neuropsychological assessments, who have sustained "mild" brain injuries and who cannot return to work frequently report sensitivity to being "near" computers and other electronic devices. They experience sensations described as "confusion" or fatigue. Unfortunately, their claims have never been tested by direct experiment. The concept of specific sensitivity in human subpopulations is not novel. Hypersensitivity, or allergy, to extremely small quantities of qualitatively specific chemical structures (e.g., peanut protein) can produce incapacitating effects. Similar sensitivities may exist to low-intensity, qualitatively different (temporally patterned) magnetic fields for some people with slightly different neuronal microstructures [31].

If all experiences and behaviors are determined by the microstructural organization of the brain and the contained electromagnetic and chemical activity, then changing the neuromatrix should allow sensitivity to and detection of physical stimuli to which the normal brain is oblivious. This may also help explain the apparent "anomalous" acquisition of information by mechanisms not known to date, the essential definition of parapsychological phenomena [32] by some individuals with unique cerebral histories [33,34]. This definition does not require the assumption of mystical forces or supernatural processes. Many of these "special" individuals have histories and experiences consistent with partial complex (temporal lobe) or limbic epilepsy as defined both by their experiences and by their unusual electroencephalographic activity [33,34].

There is, however, also a more fundamental philosophical purpose to this research derived from the queries of the 18th-century philosopher Immanuel Kant [35]. Although contemporary neuroscientists would agree that most of the details that define the information within brain space are likely to be acquired and superimposed on this *tabula rasa*, there are intrinsic constraints shared by the structures of all human brains that are determined by our genetics [36]. The nature of space and time and the operation of teleological themes, personified or maintained as abstracts, may be intrinsic properties of brain structure. The problem might be expressed as "what is really out there, beyond the sensorium and serial transformations across synapses?" To answer this question, scientists must develop a method that allows them to experimentally change the functional structure of the brain and then discern if those intrinsic properties still exist or can be modified systematically by stimuli generated in the laboratory.

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References

[1] Honchar MP, Olney JW, Sherman WR. Systemic cholinergic agents induce seizures and brain damage in lithium-treated rats. Science 1983;222:323–5.
[2] Turski L, Ikonomidou C, Turski WA, Bortolotto ZA, Cavalheiro EA. Cholinergic mechanisms and epileptogenesis. The seizures induced by pilocarpine: a novel experimental model of intractable epilepsy [review]. Synapse 1989;3:154–71.
[3] Turski WA. Pilocarpine-induced seizures in rodents—17 years on. Pol J Pharmacol 2000;52:63–5.
[4] Coulter DA, McIntyre DC, Loscher W. Animal models of limbic epilepsies: what can they tell us. Brain Pathol 2002;22:240–56.
[5] Fujikawa DG. Neuroprotective effect of ketamine administered after status epilepticus onset. Epilepsia 1995;36:186–95.
[6] Hort J, Brozek G, Mares P, Langmeier M, Komarek V. Cognitive functions after pilocarpine-induced status epilepticus: changes during silent period precede appearance of spontaneous recurrent seizures. Epilepsia 1999;40:1177–83.
[7] Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. Epilepsy Res 2000;42:117–22.
[8] Santi SA, Cook LL, Persinger MA, O'Connor RP. Normal spatial memory following postseizure treatment with ketamine: selective damage attenuates memory deficits in brain-damaged rodents. Int J Neurosci 2001;107:63–75.
[9] Stewart LS, Persinger MA. Ketamine prevents learning impairment when administered immediately after status epilepticus onset. Epilepsy Behav 2001;2:585–91.
[10] Vaillancourt LN, Persinger MA. Normalization of spatial learning despite brain damage in rats receiving ketamine after seizure-induction: evidence for the neuromatrix. Psychol Rep 2001;88:102–10.
[11] Borowicz KK, Czuczwar SJ. Effects of etomidate, ketamine or propofol, and their combinations with conventional antiepileptic drugs on amygdala-kindled convulsions in rats. Neuropharmacology 2003;45:315–24.
[12] Szakacs R, Weiczner R, Mihaly A, Krisztin-Peva B, Zador Z, Zador E. Non-competitive NMDA receptor antagonists moderate seizure-induced c-fos expression in the rat cerebral cortex. Brain Res Bull 2003;59:485–93.
[13] Fournier NM, Persinger MA. The neuromatrix and the epileptic brain: behavioral and learning preservation in limbic epileptic rats treated with ketamine but not acepromazine. Epilepsy Behav 2004;5:119–27.
[14] McKay BE, Persinger MA. Normal spatial and contextual learning for ketamine-treated rats in the pilocarpine epilepsy model. Pharmacol Biochem Behav 2004;78:111–9.
[15] Midzyanovskaya IS, Salonin DV, Bosnyakova DY, Kuznetsova GD, van Luijtelaar EL. The multiple effects of ketamine on electroencephalographic activity and behavior in WAG/Rij rats. Pharmacol Biochem Behav 2004;79:83–91.
[16] Mewasingh LD, Sekhara T, Aeby A, Christiaens FJ, Dan B. Oral ketamine in paediatric non-convulsive status epilepticus. Seizure 2003;12:483–9.
[17] Persinger MA, Makarec K, Bradley JC. Characteristics of limbic seizures evoked by peripheral injections of lithium and pilocarpine. Physiol Behav 1988;44:27–37.
[18] Persinger MA, Bureau YRJ, Peredery O. Dissociation between conditioned taste aversion and radial maze learning following seizure-induced multifocal brain damage: quantitative tests of serial vs parallel circuit models of memory. Physiol Behav 1994;56:225–35.
[19] Persinger MA, Bureau YRJ, Kostakos M, Peredery O, Falter H. Behaviors of rats with insidious, multifocal brain damage induced by seizures following single peripheral injections of lithium and pilocarpine. Physiol Behav 1993;53:849–66.
[20] Turski WA, Cavalheiro EA, Schwartz M, Czuczwar SJ, Kleinrok Z, Turski L. Limbic seizures produced by pilocarpine in rats: behavioral, electroencephalographic and neuropathological study. Behav Brain Res 1983;9:315–35.
[21] McKay BE, Persinger MA, Koren SA. Exposure to a theta-burst patterned magnetic field impairs memory acquisition and consolidation for contextual but not discrete conditioned fear in rats. Neurosci Lett 2000;292:99–102.
[22] McKay BE, Persinger MA. Application timing of complex magnetic fields delineates windows of posttraining-pretesting vulnerability for spatial and motivational behaviors in rats. Int J Neurosci 2000;103:69–77.
[23] Bausch SB, Chavkin C. Changes in hippocampal circuitry after pilocarpine-induced seizures as revealed by opioid receptor distribution and activation. J Neurosci 1997;12:477–92.
[24] Lado WE, Persinger MA. Mechanical impacts to the skulls of rats produce specific deficits in maze performance and weight loss: evidence for apoptosis of cortical neurons and implications for clinical neuropsychology. Percept Motor Skills 2003;97:115–27.

[25] Racine RJ. Modification of seizure activity by electrical stimulation: II. Motor seizure. Electroencephalogr Clin Neurophysiol 1972;32:281–94.
[26] Persinger MA, St-Pierre LS, Koren SA. Ambulatory behavior in rats following prenatal exposures to complex magnetic fields designed to interact with genetic expression. Percept Motor Skills 2001;92:183–92.
[27] Dolmetsch RE, Xu K, Lewis RS. Calcium oscillations increase the efficiency and specificity of gene expression. Nature 1998;397:933–6.
[28] Aladjalova NA. Slow electrical processes in the brain. In: Progress in brain research, vol. 7. New York: Elsevier; 1964. p. 20–207.
[29] Persinger MA, Belanger-Chellew G. Facilitation of seizures in limbic epileptic rats by complex 1 microTesla magnetic fields. Percept Motor Skills 1999;89:486–92.
[30] Olton DS, Samuelson RJ. Remembrance of places passed: spatial memory in rats. J. Exp. Psychol Anim Behav 1976;2:97–116.
[31] St-Pierre LS, Persinger MA, Koren SA. Experimental induction of intermale aggressive behavior in limbic rats by weak, complex magnetic fields: implications for geomagnetic activity and the modern habitat. Int J Neurosci 1998;96:149–59.
[32] Persinger MA. The paranormal: the patterns. New York: M.S.S. Information; 1974.
[33] Persinger MA, Roll WG, Tiller SG, Koren SA, Cook MA. Remote viewing with the artist Ingo Swann: neuropsychological profile, electroencephalographic correlates, magnetic resonance imaging (MRI) and possible mechanisms. Percept Motor Skills 2002;94:927–49.
[34] Roll WG, Persinger MA, Webster DL, Tiller SG, Cook CM. Neurobehavioral and neurometabolic (SPECT) correlates of paranormal information: involvement of the right hemisphere and its sensitivity to weak complex magnetic fields. Int J Neurosci 2002;112:197–224.
[35] Kant I. Critique of judgement [Bernard JH, Trans.]. New York: Hafner; 1966. p. 258–64.
[36] Persinger MA. On the nature of space–time perception of phenomena in science. Percept Motor Skills 1999;88:1210–6.